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|---|---|
| LUM, LEON YUN BON | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/022,631 | GEERLINGS, MAURITS W. | |
| | Examiner | Art Unit | |
| | Leon Y. Lum | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *26-43* is/are pending in the application.

4a) Of the above claim(s) *30-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. The amendments filed 27 October 2005 and 30 October 2005 are acknowledged and have been entered.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 26, 29, and 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Subramanian (US 5,292,868) in view of van Geel et al (US 5,355,394) and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986).

In the instant claims, Subramanian reference teaches attaching $^{213}Bi$ radiolabels to antibodies (i.e. targeting moiety) through a chelating agent, wherein the antibodies recognize tumor associated antigens (i.e. coupling radiolabel to a targeting moiety to form a conjugate; ligand having binding specificity for a receptor associated with said target cell; cellular diseases; diseased cells) for cancer therapy (i.e. administering to mammal). See column 1, lines 17-27; column 2, lines 51-67. In addition, Subramanian teaches conjugation with peptides. See column 10, lines 55-58.

However, Subramanian fails to teach the steps of providing a sufficient quantity of $^{225}Ac$ to produce a therapeutically effective amount of $^{213}Bi$ through radioactive decay, binding the $^{225}Ac$ onto a substrate for immobilizing $^{225}Ac$, eluting from the substrate $^{213}Bi$ produced by bound $^{225}Ac$, and that the radiolabel coupled to the targeting moiety is $^{213}Bi$, substantially free of $^{225}Ac$.

Van Geel et al reference teaches the production and recovery of $^{213}Bi$ from $^{225}Ac$, in order to obtain a radionuclide that has a short half-life of hours and has decay produces with low chemical and radiological impact. See column 1, lines 15-20 and column 2, lines 48-52; and Figure 1.

Kozak et al reference teaches eluting $\alpha$-particle emitters from nuclide generators held by resin in a polyethylene column (i.e. immobilizing substrate), in order to provide a means for easily obtaining $\alpha$-particle emitters using a disposable device. See page 263, left column, 2$^{nd}$ paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Subramanian with the production and recovery of

$^{213}$Bi from $^{225}$Ac, as taught by van Geel et al, in order to obtain a radionuclide that has a short half-life of hours and has decay produces with low chemical and radiological impact, and to modify the method of Subramanian with the step of eluting α-particle emitters from nuclide generators (i.e. $^{225}$Ac) held by resin in a polyethylene column (i.e. immobilizing substrate), as taught by Kozak et al, in order to provide a means for easily obtaining α-particle emitters (i.e. $^{213}$Bi) using a disposable device. The advantages of an alpha emitter with a short half-life and an easier technique to obtain the emitters provide the motivation to combine the steps of Van Geel et al and Kozak et al with the method of Subramanian. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in producing $^{213}$Bi from $^{225}$Ac, as taught by van Geel et al, and eluting α-particle emitters from immobilized nuclide generators, as taught by Kozak et al, in the method of Subramanian, since Subramanian teaches the use of $^{213}$Bi, and the steps taught by van Geel et al and Kozak et al are steps to produce a $^{213}$Bi.

5. Claims 26 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of van Geel et al (US 5,355,394) and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986).

In the instant claim, Macklis et al reference teaches that $^{212}$Bi-labeled radioimmunoconjugate, wherein $^{212}$Bi is bound to a monoclonal antibody conjugated to the chelating agent diethylenetriaminepentaacetic acid (i.e. coupling radiolabel to a targeting moiety to form a conjugate) is highly efficient at eradicating Thy 1.2$^{+}$ EL-4

murine lymphoma cells in vivo (i.e. target cells are in cellular diseases; administering said conjugate to a mammal; diseased cells), and this cytotoxicity is antigen selective (i.e. ligand having binding specificity for a receptor associated with said target cell). See page 1024, left column, 2nd paragraph to middle column, 2nd paragraph.

However, Macklis et al reference fails to teach the steps of providing a sufficient quantity of $^{225}Ac$ to produce a therapeutically effective amount of $^{213}Bi$ through radioactive decay, binding the $^{225}Ac$ onto a substrate for immobilizing $^{225}Ac$, eluting from the substrate $^{213}Bi$ produced by bound $^{225}Ac$, and that the radiolabel coupled to the targeting moiety is $^{213}Bi$, substantially free of $^{225}Ac$.

Van Geel et al reference teaches the production and recovery of $^{213}Bi$ from $^{225}Ac$, in order to obtain a radionuclide that has a short half-life of hours and has decay produces with low chemical and radiological impact. See column 1, lines 15-20 and column 2, lines 48-52; and Figure 1.

Kozak et al reference teaches eluting $\alpha$-particle emitters from nuclide generators held by resin in a polyethylene column (i.e. immobilizing substrate), in order to provide a means for easily obtaining $\alpha$-particle emitters using a disposable device. See page 263, left column, 2nd paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al with the production and recovery of $^{213}Bi$ from $^{225}Ac$, as taught by van Geel et al, in order to obtain a radionuclide that has a short half-life of hours and has decay produces with low chemical and radiological impact, and to modify the method of Macklis et al with the step of eluting $\alpha$-particle emitters from

nuclide generators (i.e. $^{225}Ac$) held by resin in a polyethylene column (i.e. immobilizing substrate), as taught by Kozak et al, in order to provide a means for easily obtaining α-particle emitters (i.e. $^{213}Bi$) using a disposable device. The advantages of an alpha emitter with a short half-life and an easier technique to obtain the emitters provide the motivation to combine the steps of Van Geel et al and Kozak et al with the method of Macklis et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in producing $^{213}Bi$ from $^{225}Ac$, as taught by van Geel et al, and eluting α-particle emitters from immobilized nuclide generators, as taught by Kozak et al, in the method of Macklis et al, since Macklis et al teach the use of an α-particle emitter, and the steps taught by van Geel et al and Kozak et al are steps to produce a type of α-particle emitter.

6. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Subramanian (US 5,292,868) in view of van Geel et al (US 5,355,394) and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Greer (US 4,894,364).

Subramanian, van Geel et al, and Kozak et al references have been disclosed above, but fail to teach that the conjugate is administered intermittently in fractions of the total amount, wherein a sufficient number of fractions of sufficient quantities of conjugate are administered to kill essentially all target cells, and that the total quantity of α radiation administered to the mammal is less than the total quantity necessary to kill essentially all target cells by administering a single dose of said conjugate.

Greer reference teaches administering repeated dosages with less total irradiation to achieve effective tumor kill, in order to provide a method that results in long term cures as opposed to only partial remission. See column 11, lines 59-66.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Subramanian, van Geel et al, and Kozak et al with the step of administering repeated dosages with less total irradiation to achieve effective tumor kill, as taught by Greer, in order to provide a method that results in long term cures as opposed to only partial remission. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of repeated dosages with less total radiation, as taught by Greer, in the method of Subramanian, van Geel et al, and Kozak et al, since Subramanian, van Geel et al, and Kozak et al teach radioactive elimination of tumor cells, and the repeated dosages with less total radiation taught by Greer is also used to destroy tumor cells.

7. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of van Geel et al (US 5,355,394) and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Greer (US 4,894,364).

Macklis et al, van Geel et al, and Kozak et al references have been disclosed above, and Macklis et al additionally teach the step of injecting two to four doses over four to eight hours, wherein most of the animals treated with 150 or 230 μCi were cured of their tumor burden (i.e. conjugate administered intermittently in fractions of the total

amount required kill said target cells, and a sufficient number of fractions of sufficient quantities are administered to kill essentially all target cells). See page 1024, middle column, 2nd paragraph; and 1025, right column, 1st paragraph. However, Macklis et al, van Geel et al, and Kozak et al fail to teach that the total quantity of $\alpha$ radiation administered to the mammal is less than the total quantity necessary to kill essentially all target cells by administering a single dose of said conjugate.

Greer reference teaches administering repeated dosages with less total irradiation to achieve effective tumor kill, in order to provide a method that results in long term cures as opposed to only partial remission. See column 11, lines 59-66.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al, van Geel et al, and Kozak et al with the step of administering repeated dosages with less total irradiation to achieve effective tumor kill, as taught by Greer, in order to provide a method that results in long term cures as opposed to only partial remission. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of repeated dosages with less total radiation, as taught by Greer, in the method of Macklis et al, van Geel et al, and Kozak et al, since Macklis et al, van Geel et al, and Kozak et al teach radioactive elimination of tumor cells, and the repeated dosages with less total radiation taught by Greer is also used to destroy tumor cells.

8. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Subramanian (US 5,292,868) in view of van Geel et al (US 5,355,394) and Kozak et al

(Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Turner (US 5,296,216).

Subramanian, van Geel et al, and Kozak et al references have been disclosed above, but fail to teach that said conjugate is administered continuously for a time sufficient to administer an effective amount of $^{213}Bi$ for killing said target cells in the mammal, and wherein a sufficient duration of continuous administration is maintained to kill essentially all target cells bound by said conjugate.

Turner teaches administering radiotherapy with a continuous intravenous infusion for five days, in order to prevent recurrence of cancer after surgical removal of cancer. See column 6, lines 3-14.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Subramanian, van Geel et al, and Kozak et al with the step of administering radiotherapy with a continuous intravenous infusion for five days, as taught by Turner, in order to prevent recurrence of cancer after surgical removal of cancer. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of continuous intravenous infusion for five days, as taught by Turner, in the method of Subramanian, van Geel et al, and Kozak et al, since Subramanian, van Geel et al, and Kozak et al teach radioactive elimination of tumor cells, and the continuous infusion taught by Turner also eliminates tumor cells.

9. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of van Geel et al (US 5,355,394) and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Turner (US 5,296,216).

Macklis et al, van Geel et al, and Kozak et al references have been disclosed above, but fail to teach that said conjugate is administered continuously for a time sufficient to administer an effective amount of $^{213}Bi$ for killing said target cells in the mammal, and wherein a sufficient duration of continuous administration is maintained to kill essentially all target cells bound by said conjugate.

Turner teaches administering radiotherapy with a continuous intravenous infusion for five days, in order to prevent recurrence of cancer after surgical removal of cancer. See column 6, lines 3-14.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al, van Geel et al, and Kozak et al with the step of administering radiotherapy with a continuous intravenous infusion for five days, as taught by Turner, in order to prevent recurrence of cancer after surgical removal of cancer. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of continuous intravenous infusion for five days, as taught by Turner, in the method of Macklis et al, van Geel et al, and Kozak et al, since Macklis et al, van Geel et al, and Kozak et al teach radioactive elimination of tumor cells, and the continuous infusion taught by Turner also eliminates tumor cells.

10. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of van Geel et al (US 5,355,394) and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Zamora et al (US 5,443,816).

Macklis et al, van Geel et al, and Kozak et al references have been disclosed above, but fail to teach that said ligand is a peptide.

Zamora et al reference teaches peptides that can be conjugated to a medically useful, radioactive metal ion, including bismuth, and that can be applied in vivo, in order to provide a molecule that can be frozen or lyophilized and maintained for an indefinite period before labeling with the medically useful metal ion. See column 3, lines 36-42; column 4, lines 39-47; column 9, lines 17-20; and column 20, lines 21-29.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al, van Geel et al, and Kozak et al with peptides that can be conjugated to a medically useful, radioactive metal ion, including bismuth, and that can be applied in vivo, as taught by Zamora et al, in order to provide a molecule that can be frozen or lyophilized and maintained for an indefinite period before labeling with the medically useful metal ion. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including peptides that can be conjugated to radioactive metal ions, as taught by Zamora et al, in the method of Macklis et al, van Geel et al, and Kozak et al, since Macklis et al, van Geel et al, and Kozak et al teach targeting moieties bound to an $\alpha$-particle emitting radioisotope

for radiotherapy in vivo, and the peptide taught by Macklis et al is one type of targeting moiety that can be bound to bismuth, which is a type of α-particle emitting radioisotope , and can also be applied in vivo.

11. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of Zamora et al (US 5,443,816).

Macklis et al reference has been disclosed above, but fails to teach that said ligand is a peptide.

Zamora et al reference teaches peptides that can be conjugated to a medically useful, radioactive metal ion, including bismuth, and that can be applied in vivo, in order to provide a molecule that can be frozen or lyophilized and maintained for an indefinite period before labeling with the medically useful metal ion. See column 3, lines 36-42; column 4, lines 39-47; column 9, lines 17-20; and column 20, lines 21-29.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al with peptides that can be conjugated to a medically useful, radioactive metal ion, including bismuth, and that can be applied in vivo, as taught by Zamora et al, in order to provide a molecule that can be frozen or lyophilized and maintained for an indefinite period before labeling with the medically useful metal ion. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including peptides that can be conjugated to radioactive metal ions, as taught by Zamora et al, in the method of Macklis et al, since Macklis et al teach targeting moieties bound to $^{212}Bi$ for radiotherapy in vivo, and the

peptide taught by Macklis et al is one type of targeting moiety that can be bound to radioactive bismuth and applied in vivo.

***Double Patenting***

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 26-29 and 39-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,641,471. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 of the copending application recite the limitations of claims 26-29 and 39-43 of the instant application, including the steps of killing micrometastases target cells by providing a sufficient quantity of $^{225}Ac$

immobilized on a binding medium (i.e. substrate) to produce an effective amount of $^{213}Bi$, eluting and coupling the $^{213}Bi$ to a an antibody targeting moiety (i.e. ligand having binding specificity for receptor associated with said target cell), and administering the conjugate to a mammal to permit the conjugate to contact the target cells (i.e. effectuate specific binding).

14. Claims 26-29 and 39-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 20-22 of U.S. Patent No. 6,403,771. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11 and 20-22 of the copending application recite the limitations of claims 26-29 and 39-43 of the instant application, including the steps of loading $^{225}Ac$ onto a binding medium (i.e. substrate) to yield $^{213}Bi$, eluting and coupling the $^{213}Bi$ to a ligand targeting moiety which binds specifically to a target moiety comprising a cell-associated ligand binding site (i.e. ligand having binding specificity for receptor associated with target cell), said targeting moiety forming a therapeutic radioconjugate with $^{213}Bi$, the targeting moiety being effective to deliver the radioisotope (i.e. therapeutically effective) to a pathological site in vivo (i.e. cellular disease).

***Response to Arguments***

15. On page 6 of the response filed 27 October 2005, in the Remarks section, Applicant traverses the rejection of claims 39-43 under U.S.C. 102(b) as being anticipated by Subramanian. Applicant specifically argues that Subramanian is not a valid 102(b) art since the publication date (March 8, 1994) is later than the priority date given by the Examiner (July 27, 1993). Applicant's arguments are found convincing; the application of Subramanian had been intended to be applied as 102(e) art, given the priority date of May 26, 1989, not as 102(b) art as written. Since independent claim 39 has been amended to overcome the art disclosed in Subramanian, Applicant's traversal is considered a moot point. However, the Examiner apologizes for any inconvenience and problems on Applicant's end as a result of the inadvertent mistake.

16. On pages 6-7 of the response, in the Remarks section, Applicant traverses the rejection of independent claims 26 and 29 under 35 U.S.C. 103(a) as being obvious over Subramanian in view of van Geel and Kozak. Specifically, Applicants argue two points:

(1) The combination of the claims does not entirely teach the claims, since there is no mention in the disclosures that the conjugate binds to target cells that are micrometastases having a diameter of about 1 mm or less.

(2) Kozak is directed to obtaining $^{212}$Bi from decay of thorium-228 or radium-224 and does not mention that $^{213}$Bi can be obtained from $^{225}$Ac or that $^{212}$Bi can

be obtained from $^{225}Ac$. Because of this lack of disclosure, one of ordinary skill in the art would not have had motivation to use Kozak in teaching the limitation of an immobilizing substrate to produce $^{213}Bi$ from $^{225}Ac$.

Applicant's arguments have been fully considered, but are not found convincing. With respect to Applicant's first point above, the instant claims recite the limitation "wherein said target cells are in micrometastases having a diameter of about 1 mm or less ***or are in cellular diseases***". Since the claim language has alternative language, and Subramanian teaches radiotherapy for tumor cells (i.e. cellular diseases), no disclosure of "1 mm or less" is required by the references in order to teach the instant limitation.

With respect to Applicant's second point above, Kozak is relied upon not for the specific disclosures of radioactive particles, since the claimed method of obtaining $^{213}Bi$ from $^{225}Ac$ has already been taught by Subramanian and van Geel. Instead, Kozak is relied upon for teaching of an easier way of isolating $\alpha$-particle emitters from nuclide generators, which is by immobilizing the generators in a polyethylene column and eluting the emitters. Since Subramanian already teaches a nuclide generator that produces an $\alpha$-particle emitter, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success applying the $^{225}Ac$, as taught by Subramanian, to the polyethylene column of Kozak. The motivation for combining Subramanian with Kozak, as described supra, is described in Kozak as a means for easily obtaining $\alpha$-particle emitters.

Applicant's arguments are therefore not found convincing and the previous rejection is maintained.

17. On pages 7-8 of the response, Applicant traverses the rejection of claim 26 under 35 U.S.C. 103(a) as being obvious over Macklis in view of van Geel and Kozak. Specifically, Applicants argue three points:

(1) The combination of the claims does not entirely teach the claims, since there is no mention in the disclosures that the conjugate binds to target cells that are micrometastases having a diameter of about 1 mm or less.

(2) Kozak is directed to obtaining $^{212}$Bi from decay of thorium-228 or radium-224 and does not mention that $^{213}$Bi can be obtained from $^{225}$Ac or that $^{212}$Bi can be obtained from $^{225}$Ac. Because of this lack of disclosure, one of ordinary skill in the art would not have had motivation to use Kozak in teaching the limitation of an immobilizing substrate to produce $^{213}$Bi from $^{225}$Ac.

(3) The declarations of Dr. Scheinberg and Dr. Gansow indicate that the past state of the art did not recognize the therapeutic utility of $^{225}$Ac and $^{213}$Bi. Applicants cite a portion of Dr. Scheinberg's declaration in which he mentions that "[W]e had begun by 1980 to consider using alpha emitters for therapy", but that "It was only after the urging of Dr. Geerlings that we and, later, after we presented our data showing utility, others in the field diverted our focus from bismuth-212 to actinium-255 and bismuth-213 as sources of alpha radiation therapy".

Applicant's arguments have been fully considered, but are not persuasive. With respect to Applicant's first two points above, the arguments are directed towards the same claim language and applied reference as the arguments against the rejection of claims 39-43. The Examiner has already established that the physical limitation of 1 mm diameter in micrometastasis cells does not have to be met by any applied reference, and that Kozak is a properly applied secondary reference. Macklis is similar to Subramanian with the addition of $^{225}$Ac as a disclosed $\alpha$-particle emitter generator, which provides even more motivation and expectation of success for combining Macklis and Kozak.

With respect to Applicant's third point above, the declarations submitted by Drs. Scheinberg and Gansow do not sufficiently provide evidence that overcomes the applied references. Dr. Scheinberg states in his two declarations that by 1980, he had performed investigations on alpha emitters and first focused on bismuth-212; at a later time, Dr. Geerlings directed Dr. Scheinberg to bismuth-213 with other investigators following suit. However, Dr. Scheinberg does not provide a timeline on when Dr. Geerlings' disclosure to him occurred and whether Dr. Geerlings actually had a reduction to practice of his invention as claimed. The declarations only indicate that Dr. Geerlings presented the idea of using bismuth-213 to treat and kill tumor cells. In fact, Dr. Scheinberg discloses that it was he and other investigators that actually "established utility" in using bismuth-213 (see Declaration dated April 4, 2000; page 1, last paragraph), which implies that Dr. Geerlings was not the first investigator to make and

use the invention. In addition, Dr. Scheinberg never states that Dr. Geerlings was the first investigator to actually have the invention at a date earlier than the applied references. It therefore seems as if Dr. Geerlings had not reduced the invention to actual practice before the claimed priority date, to which the applied references supercede.

Dr. Gansow states in his declaration that in 1982, he co-authored a paper that listed typical alpha emitters that can be bound to chelates, but did not include bismuth-213. In addition, Dr. Gansow indicates that in 1981, it was not known to conjugate actinium as a useful alpha emitter for radiotherapy by conjugation to monoclonal antibodies. However, at no point in his declaration does Dr. Gansow indicate anything of substance that provides evidence showing Dr. Geerlings had the claimed invention prior to the dates of the applied references. In fact, Dr. Gansow does not even mention bismuth-213, which is required in every single claim, and when he believes it was discovered as a suitable alpha emitter to be conjugated for radiotherapy.

18. In light of the statements above, Applicant's arguments traversing the applied references are not found convincing. The rejections of claims 26-29 are hereby maintained, and claims 39-43 as amended are rejected using the same references.

***Conclusion***

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on weekdays from 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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